Guidance for IRBs, Clinical Investigators and Sponsors

IRB Responsibilities for Reviewing the Qualifications of Investigators, Adequacy of Research Sites, and the Determination of Whether an IND/IDE is Needed

DRAFT GUIDANCE

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For questions regarding this draft document contact CDER, Kevin Prohaska, (301) 796-3707, or CBER, Office of Communication, Outreach and Development, (301) 827-1800 or 1-800-835-4709, or CDRH, Linda Godfrey, (301) 796-5654.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)

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Procedural

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Guidance for IRBs, Clinical Investigators, and Sponsors[1] IRB Responsibilities for Reviewing the Qualifications of Investigators, Adequacy of Research Sites, and the Determination of Whether an IND/IDE is Needed

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

FDA is issuing this guidance to remind institutional review boards (IRBs) of their longstanding role in the review of 1) the qualifications of the clinical investigator, 2) the adequacy of the facility in which the research will take place, and 3) the determination of whether an investigational new drug application (IND) or investigational device exemption (IDE) application is necessary for the proposed clinical investigation.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in agency guidances means that something is suggested or recommended, but not required.

To enhance human subject protection and reduce regulatory burden, the Department of Health and Human Services (HHS) Office for Human Research Protections (OHRP) and FDA have been actively working to harmonize the agencies' regulatory requirements and guidance for human subject research. This draft guidance document was developed as a part of these efforts and in consultation with OHRP.

II. BACKGROUND

Many of the recommendations in this guidance have appeared in other FDA guidance documents[2] or have been communicated to IRBs who have contacted the agency directly about

[1] This guidance has been prepared by FDA's Institutional Review Board Working Group, which includes representatives from FDA's Office of the Commissioner, Center for Biologics Evaluation and Research (CBER), Center for Drug Evaluation and Research (CDER), Center for Devices and Radiological Health (CDRH), and Office of Regulatory Affairs (ORA).

these issues.[3] FDA has also provided instructions to its field investigators on the types of documentation that should be reviewed during an IRB inspection to determine whether the IRB has established and followed its written procedures with respect to reviewing an investigator's qualifications, the adequacy of a site, and the determination of whether an IND or IDE is necessary.[4] FDA has compiled the advice from these various sources into this guidance to ensure that all IRBs have access to it. In addition, FDA provides guidance on how IRBs may efficiently fulfill these important responsibilities.

III. DISCUSSION

1. Must an IRB review the qualifications of clinical investigators who conduct FDA-regulated research?

Yes. Although FDA's regulations place responsibility on the sponsor to select clinical investigators who are "qualified by training and experience as appropriate experts" to investigate the test article,[5] IRBs also have a role in reviewing an investigator's qualifications.[6] The regulations at 21 CFR 56.107(a) require that an IRB be able to ascertain the acceptability of the proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice. In addition, the regulations at 21 CFR 56.111 require that an IRB determine that the proposed research satisfies the criteria for approval, including that the risks to subjects are minimized and reasonable in relation to anticipated benefits, if any, to subjects. In order to fulfill these responsibilities, the IRB needs information about the qualifications of the investigator(s) to conduct and supervise the proposed research.

Depending upon the nature and risks of the proposed research and the relationship between the IRB and the investigator or the institution where the proposed research is being conducted, this may be relatively simple and straightforward or it may entail a more involved assessment.

In many cases, the IRB may have previous experience with an investigator or institution that would allow the IRB to readily determine that the clinical investigator is appropriately qualified to conduct and supervise the proposed research. In other cases, the IRB may need additional information; however, the IRB should be able to easily obtain a statement confirming the investigator’s qualifications from an administrator of the institution. For example, for proposed research to be conducted at a hospital where only credentialed hospital staff may conduct research, the IRB may be able to rely on another office at the institution (e.g., the credentialing

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[2] ICH E6 *Good Clinical Practice: Consolidated Guidance*, *3.1.3*, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073122.pdf; and FDA Guidance, *Using a Centralized IRB Review Process in Multicenter Clinical Trials*, Section IV (in relevant part, speaks to the "capacity of the institution to conduct or support the proposed research") http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm127013.pdf.

[3] http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/RepliestoInquiriestoFDAonGoodClinicalPractice/default.htm.

[4] Compliance Program Guidance Manual (CPGM) 7348.809, Institutional Review Boards, November 28, 2011, generally, and Section III.J, K, and U.; http://www.fda.gov/downloads/ICECI/EnforcementActions/BioresearchMonitoring/UCM133768.pdf.

[5] 21 CFR 312.53(a); see also 21 CFR 812.43(a).

[6] See 21 CFR 56.102(g), (h), and (j) for definitions of IRB, investigator, and sponsor, respectively; http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm155713.htm.

office, the clinical investigator's medical department) for an assessment of the clinical investigator's qualifications. For proposed research to be conducted by a university faculty member (e.g., at an affiliated hospital or clinic), the IRB may be able to obtain a statement regarding the investigator's qualifications from the chair of the investigator's department.

On the other hand, if the reviewing IRB has no knowledge of either the clinical investigator or the institution (e.g., the IRB is not affiliated with the institution where the research will be conducted; the IRB has no previous experience with the investigator), the IRB would likely need to take additional steps to evaluate the investigator's qualifications (e.g., reviewing the curriculum vitae of the investigator, subinvestigators, and other necessary study staff; verifying professional associations and medical licensure; reviewing relevant publications).

The IRB may also need to assess the investigator's training and experience specifically related to the proposed study, particularly if the proposed research involves higher risks, vulnerable subjects, or novel technologies or surgical techniques. For such proposed research, the IRB's determination that the investigator is qualified may need to include a review of the investigator's previous specific experience both in this field (e.g., as demonstrated by recent presentations or publications), and prior experience with the test article. In addition, the IRB should pay particular attention to investigator's qualifications to conduct a study submitted for approval to the IRB if the study involves one or more of the following:

- a sponsor-investigator;[7]
- a study that is outside of the investigator's area of expertise; or
- any study design features or other characteristic(s) that may significantly increase potential risks to subjects.

The IRB may also elect to observe, or have a third party observe, the consent process and the research (21 CFR 56.109(f)), particularly if any concerns remain about the investigator's qualifications or experience.

Appropriately trained IRB support staff may assist in obtaining and assessing information about an investigator's qualifications. FDA recommends that the IRB's procedures describe the IRB's process for evaluating the investigator's qualifications to conduct and supervise the study.

2. Is any information publicly available from FDA about a clinical investigator's inspectional history?

Yes. IRBs may check the lists posted on FDA's website to determine whether a clinical investigator has been the subject of an inspection by the agency[8] and the results of such

[7] FDA's regulations (21 CFR 312.53(a) and 21 CFR 812.43(a)) require that a sponsor select clinical investigators who are "qualified by training and experience" to investigate the test article. In a sponsor-investigator (S-I) clinical trial, the S-I assumes the responsibilities of both the sponsor and the investigator (see 21 CFR 312.3(b) and 21 CFR 812.3(o)); therefore, there is no independent assessment of the clinical investigator's qualifications by the study sponsor. In this case, the IRB's review of the investigator's qualifications is particularly important to the determination that the risks to subjects are minimized and reasonable in relation to anticipated benefits, if any, to subjects.

inspections (e.g.,Warning Letters).[9] FDA also posts on its website a listing of all investigators who have been notified of the initiation of a disqualification proceeding[10] and a listing of all disqualified investigators.[11] FDA recommends that IRBs routinely check FDA's compliance and enforcement websites for information related to clinical investigator inspections and disqualification proceedings.

3. Must an IRB review the adequacy of the research site?

Yes. FDA's regulations require that before an IRB can approve research covered by the regulations, the IRB must be able to ascertain the acceptability of the proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice.[12] The regulations also require that each IRB have sufficient information to determine that the proposed research satisfies the criteria for approval.[13]

In the great majority of instances, an IRB will likely be familiar with the research site or institution at which the clinical investigator has proposed to conduct the research; in such cases, additional assessment of a site's adequacy will probably not be necessary (for example, if the research is to be conducted at the IRB's affiliated institution). In other cases, the IRB may need additional information in order to assess the site where the proposed research will take place to ensure it can adequately execute the protocol requirements. Depending upon the nature and risks of the proposed research and the IRB's prior knowledge of or relationship to the institution or other site at which the research will take place, this may be relatively simple and straightforward or it may entail a more involved assessment.

For example, if a proposed clinical investigation involves administration of medical procedures by qualified healthcare providers using medical equipment, the IRB should be prepared to assess the adequacy of the facility's staff and equipment, including the availability of emergency or specialized care if the need should arise. If the proposed research site is part of a major medical institution, the IRB would likely be able to simply note that fact. If, however, the IRB is unfamiliar with the proposed investigational site (e.g., research facility, hospital, physician's office, dental clinic), the IRB would likely need to confirm whether the site is appropriately staffed and equipped to conduct the proposed research. The IRB should be able to obtain a statement from an appropriate person or persons at the research site or institution stating that the facilities are adequate. Alternatively, the IRB could ask that the investigator provide a

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[8] Lists of investigators who have been inspected by FDA for CDER are posted at: http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ComplianceEnforcement/default.htm; for CBER: http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ComplianceActivities/ucm165743.htm. Investigators who conducted a device study from 2009 to present are included in the Inspection Classification Database maintained by FDA's Office of Regulatory Affairs at: http://www.accessdata.fda.gov/scripts/inspsearch.

[9] See the agency's Electronic Reading Room, including Warning Letters (http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/default.htm).

[10] See http://www.fda.gov/RegulatoryInformation/FOI/ElectronicReadingRoom/ucm092185.htm.

[11] See http://www.fda.gov/ICECI/EnforcementActions/DisqualifiedRestrictedAssuranceList/ucm131681.htm.

[12] 21 CFR 56.107(a).

[13] 21 CFR 56.111(a).

description of the facility where the research will take place, including its staffing and resources relevant to the research under review.

4. What are the IRB's responsibilities with respect to verifying the determination of whether an IND or IDE is required for an FDA-regulated investigation?

The IRB's specific responsibilities vary, depending on the product that is the subject of the study; however, in general, the IRB should ask the investigator whether he/she considered the need to obtain an IND or IDE and the basis for any determination as to whether an IND/IDE is or is not needed.

Drug and Biologics Studies. FDA regulations require sponsors and clinical investigators to determine whether an IND is necessary for a particular study.[14] The sponsor (or sponsor-investigator of an individual investigator-initiated study) should be able to determine whether the IND regulations apply to a planned clinical investigation as required under 21 CFR 312.2(a). If a sponsor is uncertain, however, we recommend that the sponsor contact the appropriate review division (i.e., for the therapeutic area being studied) in the appropriate FDA Center for advice about whether the IND regulations apply (21 CFR 312.2(e)).

When reviewing a proposed study, IRBs should ask the clinical investigator whether an IND is or is not required and the basis for the determination. If the sponsor or investigator has determined that an IND is not needed, the IRB may request that the investigator provide a copy of any available documentation about the need for an IND (e.g., letter from the sponsor or FDA, other basis for that determination). If during its initial review of a study, the IRB questions whether an IND is necessary, but is unable to resolve this issue, the IRB should follow its procedures for resolving controverted issues (e.g., notifying the clinical investigator in writing of the IRB's concerns[15] and delaying approval of the study until the matter is resolved). FDA issued for public comment the *Draft Guidance for Industry: Investigational New Drug Applications (INDs) — Determining Whether Human Research Studies Can Be Conducted Without an IND.*[16] When finalized, the guidance will represent FDA's current thinking on this topic.

Organizational charts listing the review divisions for the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) and their phone numbers are available on FDA's website.[17] If the relevant review division is not known, the sponsor may contact CDER or CBER directly:

CDER: Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration

[14] See 21 CFR 312.2, 312.20, 312.50, and 312.60. Studies that are exempt from the IND requirements are required, however, to comply with 21 CFR Part 50 (Protection of Human Subjects) and Part 56 (Institutional Review Boards).
[15] 21 CFR 56.109(e)
[16] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM229175.pdf.
[17] CDER: http://www.fda.gov/AboutFDA/CentersOffices/OrganizationCharts/ucm135674.htm;
CBER: http://www.fda.gov/AboutFDA/CentersOffices/OrganizationCharts/ucm135943.htm.

10001 New Hampshire Avenue, 4th Floor
Silver Spring, MD 20993
(Tel) 301-796-3400

CBER: Office of Communication, Outreach and Development[18]
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike, Suite 200N
Rockville, MD 20852-1448
(Tel) 800-835-4709 or 301-827-1800

Device Studies. The sponsor is responsible for determining whether submission of an IDE application to FDA is required before a study may proceed.[19] The IDE regulations (21 CFR 812) describe three types of device studies: significant risk (SR), nonsignificant risk (NSR), and exempt studies.[20] SR device studies must have an IDE application approved by FDA before they proceed, and they must follow all of the IDE requirements.[21] NSR device studies must follow the abbreviated IDE requirements at 21 CFR 812.2(b) and do not require submission of an IDE application to FDA.

The sponsor is responsible for making the initial risk determination, SR or NSR, and presenting it to the IRB.[22] If the sponsor has determined that a device study is NSR, the IRB must review the sponsor's determination.[23] If the IRB disagrees with the sponsor's NSR assessment and decides the study is SR, the IRB must inform the clinical investigator and, where appropriate, the sponsor.[24]

FDA is available to assist sponsors, investigators, and IRBs in making these determinations. For information on how to request such assistance, please see the guidance *Procedures for Handling Inquiries Regarding the Need for an Investigational Device Exemptions Application for Research Involving Medical Devices.*[25] Sponsors, clinical investigators, and IRBs who need assistance in making a risk determination for a medical device may also contact:

IDE Staff
Office of Device Evaluation
Center for Devices and Radiological Health
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

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[18] http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CBER/ucm106001.htm.
[19] 21 CFR 812.2(b)(1)(ii).
[20] With the exception of 21 CFR 812.119, exempt studies are not subject to the IDE regulations. 21 CFR 812.2(c). Exempt studies are required to comply with 21 CFR Part 50 (Protection of Human Subjects) and Part 56 (Institutional Review Boards).
[21] 21 CFR 812.20(a)(1) and (2).
[22] 21 CFR 812.2(b)(1)(ii).
[23] 21 CFR 812.2(b)(1)(ii).
[24] 21 CFR 812.66.
[25] http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm126598.htm.

(Tel) 301-796-5640

Based on the information provided, FDA will determine if a device study is SR, NSR, or exempt from the IDE requirements found in 21 CFR Part 812. If FDA makes the SR or NSR determination for a study, the agency's determination is final. Additional information may be found in the *Information Sheet Guidance for IRBs, Clinical Investigators, and Sponsors - Significant Risk and Nonsignificant Risk Medical Device Studies.*[26]

Although not required by the regulations, FDA recommends that the IRB have written procedures that explain how the IRB makes a SR/NSR determination.

[26] http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126418.pdf.